Hodgkin lymphoma

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Introduction

Hodgkin lymphoma (HL) represents approximately 10% of all lymphoma cases diagnosed in the United States. This group of diseases usually presents with painless lymphadenopathy involving the neck and chest. Systemic symptoms of fevers, night sweats, and unexplained weight loss may occur in patients with advanced-stage disease (Figure 21-1). Today, the majority of patients with HL are cured with combination chemotherapy with or without radiation. In addition, several novel targeted therapeutic agents have been approved by the United States Food and Drug Administration (FDA). Given the long-term survival of patients with HL, efforts continue to focus on reducing late, treatment-related toxicities.

Epidemiology

In 2021, approximately 8830 patients are expected to be diagnosed with HL in the United States, and 960 patients are expected to die from this malignancy. The disease has a bimodal age distribution with one peak in the early 20s and the second in the mid-70s. There is a slight male predominance (male:female incidence ratio of 1:3).

Pathology

HL is a monoclonal lymphoid neoplasm derived from B cells in most cases and is divided into 2 distinct entities, classical Hodgkin lymphoma (cHL) (95% of cases) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). The malignant cell in cHL, the Hodgkin Reed-Sternberg (HRS) cell, is a large, bilobed cell with 2 or more nuclei with eosinophilic nucleoli. HRS cells are derived from germinal center B lymphocytes but lack a B-cell receptor and several B-cell associated genes and proteins. HRS cells account for the minority of cells in affected lymph nodes and are surrounded by a background of mixed inflammatory cells. In cHL, the HRS cells express CD30 and CD15. Other B-cell markers are typically reduced or absent, including CD20, CD19, and transcription factors OCT-2 and BOB1. PAX-5 also is expressed in HRS cells in most cases. PAX-5 can be helpful in distinguishing cHL from anaplastic large-cell lymphoma. Other B- and T-cell markers, including CD45, are typically absent. Epstein-Barr virus (EBV), as evidenced by LMP-1 or EBV small nuclear transcripts, is found in a subset of cHL, including the majority of

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Off-label drug use: Rituximab for the treatment of lymphocyte-predominant Hodgkin lymphoma; HDAC inhibitor and lenalidomide in relapsed/refractory Hodgkin lymphoma.

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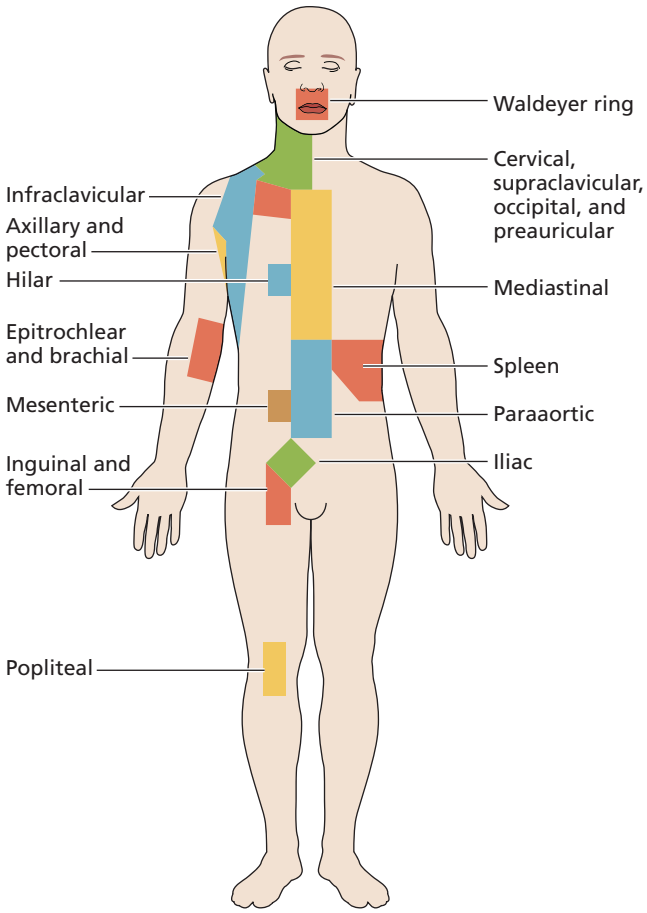


Figure 21-1 Nodal map. The Waldeyer ring includes the pharyngeal tonsil (adenoids), palatine tonsil, and lingual tonsil (base of tongue).

cases of mixed cellularity, and nearly all cases of lymphocyte depleted (LD) HL.

Within cHL, there are 4 histologic subtypes: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte rich (LR), and LD. NS HL is composed of nodular areas with fibrous bands. The HRS cells may be rare in NS but also may be found in sheets (the *syncytial variant* of NS). In the MC variant, HRS cells are more abundant and are surrounded by neutrophils, eosinophils, macrophages, and plasma cells without areas of fibrosis. The nodal appearance is most commonly diffuse. LR HL typically appears nodular but also can be diffuse. Typical HRS are present in LR HL, and the background is composed predominantly of small lymphocytes. The least common subtype, LD HL, has a diffuse histologic appearance with a large number (sheets) of HRS cells in a background of fibrosis and necrosis with few inflammatory cells.

NLPHL is morphologically and immunophenotypically distinct from cHL. The lymphocyte-predominant

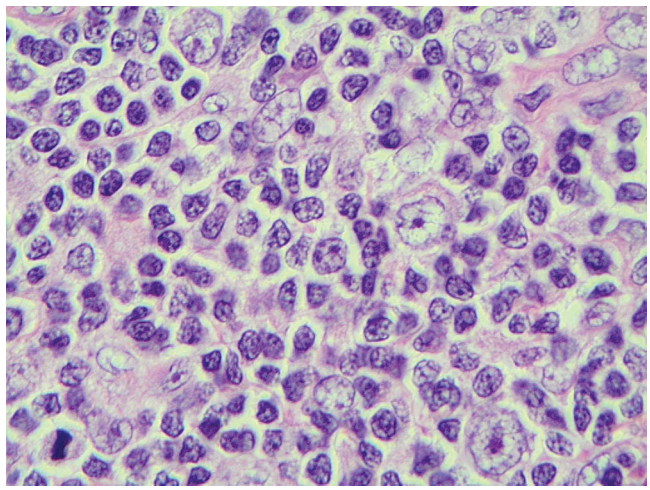
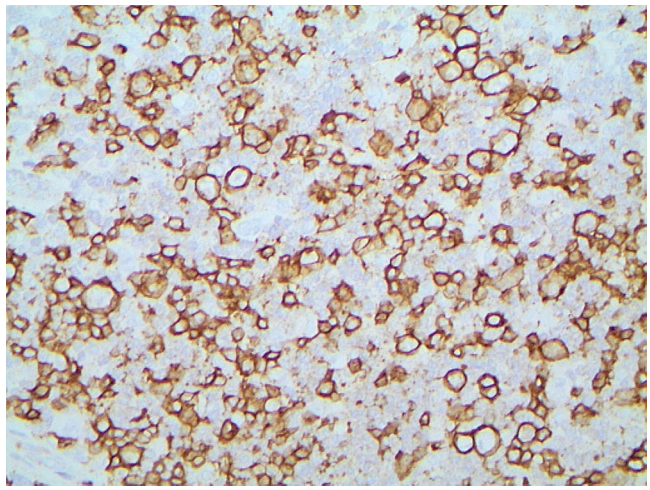


Figure 21-2 LP or popcorn cells in NLPHL with typical folded, multilobulated nucleus.

(LP) cells of NLPHL are popcorn cells, with lobulated, vesicular nuclei with multiple small nucleoli located peripherally that are found in follicular structures with a partial loss of the B-cell phenotype (Figure 21-2). NLPHL is derived from antigen-selected B cells and expresses typical germinal center B-markers including BCL-6. Unlike the classic HRS cell, LP cells are typically $CD30^-$ and CD15-negative, and positive for $CD20^+$, $CD79a^+$, PAX-5, and OCT-2 (Figure 21-3). The background lymphocytes are predominantly small $CD20^+$ B cells with rare eosinophils, neutrophils, and plasma cells (Figure 21-4). Surrounding the LP cells are $CD4^+$ T-cell rosettes as well as CD21-positive follicular dendritic cells, consistent with the germinal center derivation of this malignancy.

Figure 21-3 CD20 staining on large LP cells in NLPHL.



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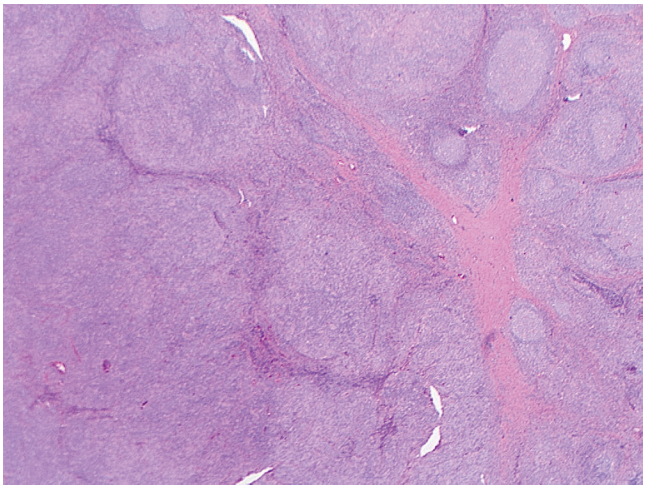

Figure 21-4 Low power view of NLPHL.

Pathogenesis

NLPHL and cHL are characterized by constitutive activation of the nuclear factor κB pathway. cHL also demonstrates increased signaling through the Janus kinase–signal transducer and activation of transcription signaling (JAK/STAT) pathway. HRS use immunosuppressive mechanisms to promote survival through programmed cell death 1 (PD-1) signaling as demonstrated by ubiquitous expression of PD ligands 1 and 2 on their cell surface. Genetic analyses have revealed 97% of patients had 9p24.1 alterations, resulting in the upregulation of the target genes: programmed death 1 ligands (PD-1 ligands) and JAK2. Epstein-Barr virus latent membrane protein 1 also induces PD-L1 expression via AP-1 and JAK/STAT pathways, highlighting an additional viral basis for PD-L1 upregulation in EBV-associated cHL.

KEY POINTS

- Approximately 8830 new cases of HL are diagnosed per year in the United States.
- cHL is typically CD30, CD15, and Pax-5 positive with other negative B-cell markers, whereas NLPHL is CD30 and CD15 negative, with CD19, CD20, CD45, and CD79a positivity.
- Genetic alterations of 9p24.1 encoding for PDL-1/-2 are present in 97% of cHL cases.

Clinical presentation

Patients with cHL often present with nontender lymphadenopathy. The neck is the most commonly involved site of disease. B symptoms, defined as fevers >38.0 °C, drenching night sweats, and involuntary weight loss of >10% of body weight in the preceding 6 months, occur in a proportion of patients with advanced-stage disease but are present in <10% to 20% of patients with early-stage disease. Pruritus is seen in 10% to 15% of patients. Although it occurs rarely (<5% of cases), patients may experience intense pain in the sites of disease upon alcohol ingestion.

NS cHL accounts for 70% of cases in the Western world. Males and females are affected in equal proportion and, at diagnosis, most patients are between the ages of 15 and 35 years. Mediastinal involvement, which may be bulky, is more common in NS cHL, and patients may present with respiratory symptoms. Mixed-cellularity cHL is the second most common subtype in the industrial world, representing 20% of cHL. There is a male predominance. Peripheral lymphadenopathy is more common than mediastinal disease, and there is orderly progression from one lymph node basin to the next. LR cHL accounts for 5% of all cases. Patients typically present with early-stage disease affecting peripheral nodes.

LD cHL is the least common subtype at 1% of cases in the Western world. The median age of onset is in the 30s, and males are more often affected. It is more common in the industrial world and in HIV-infected individuals. Extranodal and intra-abdominal disease, advanced-stage disease, and systemic symptoms are common.

There are also racial differences in clinical presentation, with White patients presenting at a younger age with NS HL and early-stage disease and Hispanic patients presenting at older ages with MC HL and advanced-stage disease.

Staging and workup

To make a definite diagnosis of HL, an adequate tissue biopsy is critical. Fine-needle aspirate is not adequate to evaluate architecture and establish the histologic subtype. Incisional or excisional biopsy is preferred, although image-guided core-needle biopsy in patients without peripheral lymphadenopathy may yield sufficient tissue.

Staging should be performed with [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography/computerized tomography (PET/CT) scanning. PET/CT improves the accuracy of staging compared with CT scans alone and is the preferred imaging modality in cHL., Bone marrow biopsies are not necessary as part of the initial staging procedures for most patients with cHL younger than 60 years old. Ann Arbor staging classification should be used for disease localization (Table 21-1); however, patients should be treated as having limited (I, II nonbulky) or extensive (III-IV) disease, with stage II bulky disease and those with multiple lymph node regions involved generally classified as extensive disease

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Table 21-1 Staging of Hodgkin lymphoma

Stage I. Involvement of one lymph node region.
Stage II. Involvement of 2 or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be lateralized and, when involved on both sides, constitute stage II disease. For the purpose of defining the number of anatomic regions, all nodal disease within the mediastinum is considered to be a single lymph node region, and hilar involvement constitutes an additional site of involvement.
Stage III. Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm.
Stage IV. Diffuse or disseminated involvement of one or more extranodal organs or tissue beyond that designated E, with or without associated lymph node involvement.
All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant unexplained fever, drenching night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months before diagnosis.
The designation "E" refers to extranodal contiguous extension (ie, proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. More extensive extranodal disease is designated stage IV.
The subscript "X" is used if bulky disease is present. This is defined as a mediastinal mass with a maximum width that is equal to or greater than 1/3 of the internal transverse diameter of the thorax at any level or >10 cm maximum dimension of a nodal mass.

based on the updated 2014 Lugano criteria. Bulky disease is defined as a single nodal mass measuring at least 10 cm in greatest diameter or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT. The absence (A) or presence (B) of B symptoms should be recorded.

For restaging using PET/CT, the Deauville 5-point scale reading system (Table 21-2) allows for more accurate measurement of response by using a categorical scoring system with a continuous variable. Values are recorded by comparing disease uptake to a reference organ with generally consistent metabolic activity, reducing interreader and interdevice inconsistencies.

Initial laboratory assessment should include a complete blood count (CBC) with differential and assessment of renal and hepatic function, including albumin, before initiating chemotherapy. HIV testing should be considered. Erythrocyte sedimentation rate (ESR) commonly is elevated and is prognostic in early-stage disease. Lactate dehydrogenase is rarely elevated, except in patients with extensive, advanced-stage disease. Pulmonary function testing and assessment of cardiac function should be obtained before the initiation of chemotherapy whenever possible but should not delay the initiation of therapy in a young patient without comorbidities. Counseling on fertility preservation and referral to a fertility specialist as appropriate should be performed as early in the workup as possible.

Table 21-2 Deauville 5-point scale criteria for evaluation of restaging PET

Score	Criterion
1	No uptake
2	Uptake ≤ mediastinum
3*	Uptake > mediastinum but ≤ liver
4	Moderately increased uptake > liver
5	Markedly increased uptake > liver

*Most common negative versus positive cutoff in clinical trials for early-stage Hodgkin lymphoma (scores 1-2 versus 3-5). Most common negative versus positive cutoff in clinical trials for advanced-stage Hodgkin lymphoma (score 1-3 versus 4-5).

KEY POINTS

- PET/CT scans are recommended for initial and interim staging evaluation.
- Based on the updated Lugano classification, bone marrow biopsies are not recommended for initial staging in most patients.
- PET scans should be scored using the Deauville 5-point scale reading system to limit interreader variability.

Frontline therapy for early-stage HL

CLINICAL CASE

A 24-year-old woman presents with a persistent dry cough of 2 months duration. She has no weight loss, fever, or night sweats. A chest x-ray reveals a widened mediastinum, and a subsequent chest CT is notable for a 3.5 cm anterior mediastinal mass. Mediastinoscopy and biopsy are performed and reveal classical HL, NS subtype with neoplastic HRS cells expressing CD30, CD15, and negative for CD20. EBV small nuclear transcripts are negative. PET and CT scans demonstrate disease localized to the mediastinum and bilateral hilum. Laboratory studies show a mild leukocytosis at 12.5 with 80% neutrophils and 10% lymphocytes with an otherwise normal CBC. ESR is 25. PET and CT scans after 2 cycles of therapy show mediastinal uptake less than blood pool, and she completes 4 cycles of doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy followed by involved-site radiotherapy (ISRT) to 30 Gy.

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Overall, the prognosis of early-stage cHL, using currently available therapies, is excellent, with >85% of patients being cured with initial therapy and >95% of patients alive at 5 years. There remains debate regarding use of combined modality therapy (CMT) (ie, chemotherapy followed by consolidative radiotherapy) versus using chemotherapy alone. The more common therapeutic recommendation in Europe includes combined modality therapy given its superior freedom from treatment failure (FFTF). There has been increasing use of chemotherapy alone in North America for HL patients with early-stage disease. Chemotherapy alone is associated with a higher risk of relapse (4% to 8%) but likely has less long-term toxicity compared with combined modality treatment. Overall survival (OS) has not been shown to be different, in part because of the salvageability with effective subsequent therapies.

Therapy with ABVD is the favored chemotherapy for HL in most centers in terms of efficacy and toxicity, including risk of secondary malignancies and infertility. The majority of patients receiving ABVD develop significant granulocytopenia. Despite this, retrospective data suggest that the risk of febrile neutropenia is quite low, <1% per cycle. The majority of HL patients may be treated safely with full-dose therapy without growth factors and without dose delays because of neutropenia. For patients who develop febrile neutropenia, granulocyte colony-stimulating factor (G-CSF) should be administered for the minimal number of days to support the white blood cell count.

Bleomycin-associated pneumonitis is seen in 1% to 3% of patients overall and up to 20% to 30% of patients older than 60 to 65 years of age receiving ABVD, with compromised renal function being a prominent risk factor. There are not well-studied guidelines for prospective monitoring of patients receiving bleomycin. Baseline pulmonary function tests may be obtained before chemotherapy. A low baseline diffusing capacity (DLCO) should be corrected for baseline hemoglobin levels and interpreted carefully in patients with extensive disease in the chest. Collectively, a high index of suspicion is critical for the early recognition of bleomycin lung toxicity (BLT). Patients who develop cough and or dyspnea on exertion with or without fevers should be evaluated promptly by physical examination with ambulation and/or at rest for the presence of basilar crackles and oxygen desaturation. Chest x-ray may reveal an interstitial pattern of abnormality, and a decline in the DLCO on pulmonary function testing is typical. Bleomycin should be discontinued promptly and steroids should be administered for patients with significant symptoms or hypoxemia. The value of serial pulmonary function testing has not been demonstrated clearly but may show asymptomatic decreases in DLCO.

Radiation therapy

Given the associated long-term toxicities, particularly secondary malignancies and cardiac dysfunction, and the improvement in outcomes with the addition of effective chemotherapy, the extent and dose of radiotherapy (RT) used for the treatment of HL have decreased over time. By definition, extended field radiotherapy, also known as *subtotal nodal radiotherapy*, included both the involved lymph nodes and the grossly normal adjacent lymph nodes. Typical extended fields were the mantle field and the inverted Y field. Involved-field radiotherapy (IFRT), which encompasses only the clinically involved lymph nodes, replaced extended field radiotherapy based on the results of 2 randomized studies. Involved-node radiotherapy (INRT) and ISRT are the major forms of RT currently used for HL. These forms of RT further minimize the radiation exposure to uninvolved tissue, and thus decrease potential long-term toxicities from RT.

The dose of RT is dependent in part on the stage and risk of early-stage disease (ie, favorable versus unfavorable). Current studies typically employ 20 to 30 Gy of ISRT for nonbulky disease and 30 to 36 Gy of ISRT for bulky disease.

Risk stratification

A number of prognostic indicators have been identified in early-stage cHL and are employed in clinical trials to risk stratify patients (Table 21-3). The German Hodgkin

Table 21-3 Risk factors in early-stage Hodgkin lymphoma*

Organization	Risk factors
EORTC	Age >50 years
	LMA (>1/3 maximum intrathoracic diameter)
	ESR >50 without B sx
	ESR >30 with B sx
	>3 lymph node groups
GHSG	LMA (>1/3 maximum intrathoracic diameter)
	ESR >50 without B sx
	ESR >30 with B sx
	Extranodal extension
	>2 lymph node groups
NCCN	LMA (>1/3 maximum intrathoracic diameter)
	ESR >50
	Any B symptoms
	>3 lymph node groups
	Any bulky disease >10 cm

B symptoms (sx), fevers, drenching night sweats, unexplained weight loss; LMA, large mediastinal mass.

*It is important to highlight that the nodal maps differ based on GHSG versus EORTC studies.

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Study Group (GHSG) scale includes 5 risk factors: (1) bulky mediastinal disease as defined by more than 1/3 of the maximal intrathoracic cavity, (2) ESR of 30 in the presence of B symptoms or (3) ≥50 without B symptoms, (4) extranodal extension of disease, and (5) 3 or more lymph node sites of involvement. The European Organisation for Research and Treatment of Cancer (EORTC) scale includes (1) age ≥50 years, (2) bulky mediastinal disease, (3) ESR of 30 in the presence of B symptoms or (4) ≥50 without B symptoms, and (5) 4 or more nodal sites of involvement. The National Comprehensive Cancer Network (NCCN) scale is similar to the EORTC with the exception of (1) it omits age as a prognostic factor, (2) includes B symptoms regardless of the ESR, and (3) uses an ESR >50 as the cutoff for having unfavorable disease. The presence of bulky mediastinal disease is considered to be unfavorable by all groups. Basically, to summarize, all 3 scales use the ESR level, the presence or absence of B symptoms, bulky mediastinal disease, and number of nodal sites to determine if a patient is considered early-stage favorable or unfavorable. In Canadian and some US cooperative group studies, patients with stage IIB disease are considered to have advanced-stage disease.

Early favorable disease

The EORTC H8F and GHSG HD10 established combined modality therapy as a standard of care in early favorable HL. The GHSG HD10 study randomized 1370 patients without risk factors to combined modality therapy with 4 versus 2 cycles of ABVD with 30 Gy versus 20 Gy of IFRT. With a median follow-up of 7.5 years, there was no difference in FFTF or OS at 5 years in any of the 4 groups, and toxicity was comparable between all arms. The authors concluded that ABVD for 2 cycles followed by 20 Gy of IFRT was standard therapy for early-stage favorable HL.

In the follow-up HD13, the GHSG examined the relevance of bleomycin and dacarbazine in the ABVD regimen in patients with favorable-risk early-stage disease. Patents were randomized to 2 cycles of ABVD, omission of bleomycin, dacarbazine, or both followed by 30 Gy of IFRT. The AV and ABV arms were closed early because of adverse events. The 5-year FFTF was 93% in ABVD versus 81%, 89%, and 77%, respectively, in the ABV, AVD, and AV arms. ABVD remained the standard, with AVD showing the least reduction in efficacy of the 3 remaining arms. See Table 21-4 for a summary of notable trials in early favorable HL.

Chemotherapy-only approaches have also been used effectively in early-stage favorable cHL. Two notable studies showed durable remissions with a chemotherapy-only approach using PET-adapted therapies. The first study, referred to as the RAPID trial, treated early-stage nonbulky cHL patients with 3 cycles of ABVD followed by a PET scan. Patients with a negative PET scan were randomized to receive IFRT or no further treatment. After a median follow-up of 60 months, the 3-year progression-free survival (PFS) was 94.6% in the radiation group versus 90.8% in the no further treatment group. The difference between the 2 groups was not statistically significant. The second study was done by the Cancer and Leukemia Group B cooperative group. All patients in this study received 2 cycles of standard ABVD followed by a PET scan. Patients with a negative PET scan went on to receive 2 additional cycles of ABVD and no radiation therapy. After a median follow-up of 3.8 years, the 3 year PFS was 91%. See the section on "Chemotherapy alone and PET-adapted therapy" for further information.

Early unfavorable disease

Whereas ABVD and CMT are considered standard in early favorable cHL, the role of radiation and more intensive therapies like the GHSG-derived bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen are not as clear. HD11 assessed whether more intensive chemotherapy with BEACOPP could improve outcomes compared to ABVD. Patients received 4 cycles of BEACOPP or ABVD followed by 20 or 30 Gy of IFRT. There were no differences between the chemotherapy arms, so the less-toxic ABVD combined with 30 Gy is more often used in this setting.

The subsequent HD14 study examined the role of incorporating initial treatment with escalated BEACOPP followed by ABVD to maximize efficacy and reduce treatment-related toxicity. Patients were randomized to standard therapy with 4 cycles of ABVD versus 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD (2 + 2). All patients received 30 Gy of IFRT. The 2 + 2 arm resulted in improvement in the primary endpoint of 5-year FFTF at 95% versus 88% ($P < 0.001$) in the standard arm. The OS, however, was excellent in both arms at 97%, highlighting the ability to salvage patients initially treated with ABVD. Grade 3 toxicity was significantly more prominent in the BEACOPP arm. See Table 21-5 for a summary of randomized trials in early unfavorable HL.

Chemotherapy alone and PET-adapted therapy

Given the late effects of RT, including secondary malignancies (especially breast cancer in women younger

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Table 21-4 Favorable early-stage I-II Hodgkin lymphoma: notable trials*

Trial	No. of patients	Treatment regimens	Outcome	
CALGB 50604	149	2 ABVD then PET scan. PET negative: 2 ABVD PET positive: 2 escBEACOPP + IFRT	3-year PFS 91% 66%	—
RAPID study	571	3 ABVD then PET scan. PET negative: IFRT No further therapy	3-year PFS 94.6% 90.8% *P* = NS	3-year OS 97.1% (IFRT) versus 99% *P* = NS
GHSG HD10	1370	2 ABVD + IFRT (30 Gy) 2 ABVD + IFRT (20 Gy) 4 ABVD + IFRT (30 Gy) 4 ABVD + IFRT (20 Gy)	5-year FFTF 91% to 92% overall *P* = NS	5-year OS 96% to 97% overall *P* = NS
NCI-C/ECOG	276	ABVD 4 to 6 cycles ABVD 2 cycles + STLI	5-year EFS 88% 92% *P* = 0.09	5-year OS 95% 92% *P* = NS
GHSG HD13	1502	2 ABVD + 30 Gy IFRT 2 ABV + 30 Gy IFRT 2 AVD + 30 Gy IFRT 2 AV + 30 Gy IFRT	5-year FFTF 93.1% 81.4% 89.2% 77.1%	5-year OS 97.6% 94.1% 97.6% 98.1% *P* = NS
GHSG HD16	628 (PET negative)	2 ABVD + 20 Gy IFRT 2 ABVD then PET PET negative: no further therapy	5-year PFS 93.4% 86.1% HR = 1.78	5-year OS 98.1% 98.4% HR = 0.37
EORTC/ LYSA/FIL H10F	465 (favorable, PET negative)	a) ABVD + INRT b) ABVD	5-year PFS 87% 99% HR = 15.8	5-year OS 100.0% 99.6%
UK NCRI RAPID (75% favorable)	602	PET negative ABVD × 3 ABVD × 3 + IFRT PET positive ABVD × 3 + IFRT	3-year PFS 91% 95%, *P* = 0.23 85%	3-year OS 97.1% 99%, *P* = NS 87.6%

ECOG, Eastern Cooperative Oncology Group; LYSA, Lymphoma Study Association; NCI-C, National Cancer Institute of Canada; NS, not significant; STLI, subtotal nodal irradiation; UK NCRI, United Kingdom National Cancer Research Institute.

*See text for definitions of early-stage category.

than 30 years old and cardiovascular disease), a handful of studies have evaluated the use of chemotherapy-only in Hodgkin lymphoma. PET-directed approaches tested the ability to omit radiation in those achieving responses in the RAPID-UK and EORTC H10 studies. In the RAPID-UK and EORTC H10 studies.

The United Kingdom (UK) RAPID trial assessed PET-directed deescalation of therapy in patients with stage IA/IIA HL. PET scans were performed after 3 cycles of ABVD. PET-negative patients (Deauville score of 1 or 2) were randomized to receive no further therapy versus IFRT and PET-positive patients (Deauville score of 3 to 5) received consolidation with IFRT. At a median follow-up of 60 months, 3-year PFS rates for PET-3-negative patients who received CMT versus chemotherapy alone were 94.6% versus 90.8%, respectively, which exceeded the prespecified noninferiority boundary. Altogether, these data suggest noninferiority was *not present* for 3-year PFS, although outcomes were excellent in both groups. Overall survival at 3 years was 97% in IFRT arm and 99% in the non-IFRT arm, which was nonsignificant.

The H10F and H10U studies, led by the EORTC, randomized favorable (F) and unfavorable (U) early-stage HL patients (using EORTC definitions) to PET-based versus non–PET-based treatment strategies. At preplanned interim analysis, more early progressions were noted in the chemotherapy-only arm than in the CMT arm for both F and U cohorts. Therefore, the study was amended to add INRT to all treatment

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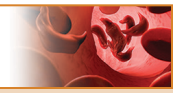
Table 21-5 Unfavorable early-stage I-II Hodgkin lymphoma: randomized chemotherapy studies*

Trial	No. of patients	Treatment regimens	Outcome	
GHSG HD11	1395	4 ABVD + IFRT (30 Gy) 4 ABVD + IFRT (20 Gy) 4 BEACOPP-base + IFRT (30 Gy) 4 BEACOPP-base + IFRT (20 Gy)	5-year FFTF 88.3% 81.1% 87.0% 86.8% *P* = *NS**	5-year OS 94.3% 93.8% 94.6% 95.1% *P* = *NS*
			* Significant difference between ABVD and BEACOPP in 20-Gy arms (*P* = 0.02)	
NCI-C/ECOG	276	ABVD 4-6 cycles ABVD 2 cycles + STLI	5-year EFS 88% 92% *P* = 0.09	5-year OS 95% 92% *P* = NS
EORTC H9U	808	6 ABVD + IFRT (30 Gy) 4 ABVD + IFRT (30 Gy) 4 BEACOPP-base + IFRT (30 Gy)	4-year EFS 91% 87% 90% *P* = NS	4-year OS 95% 94% 93% *P* = NS
GHSG HD14	1216	4 ABVD + IFRT (30 Gy) 2 escBEACOPP + 2 ABVD + IFRT (30 Gy)	5-year FFTF 87.7% 94.8% *P* < 0.001	5-year OS 96.8% 97.2% *P* = NS
EORTC/LYSA/ FIL H10U	594 (unfavorable, PET negative)	6 ABVD 4 ABVD + INRT	5-year PFS 89.6% 92.1% HR = 1.45	5-year OS 98.3% 96.7%
EORTC/LYSA/ FIL H10F/U	361 patients PET positive	escBEACOPP ABVD + INRT	5-year PFS 91% 77.4% HR = 0.42; *P* = 0.002	5-year OS 96.0% 89.3% *P* = 0.062
GHSG HD17 (NCT00736320)	1100	Standard arm: 2 escBEACOPP + 2 ABVD + IFRT (30Gy) Experimental arm: 2 escBEACOPP + 2 ABVD PET positive: 30-Gy INRT PET negative: No RT	5-year PFS 97.3% 95.1% HR = 0.523	5-year OS 98.0.8% *P* = NS

base, baseline; ECOG, Eastern Cooperative Oncology Group; LYSA, Lymphoma Study Association; NCI-C, National Cancer Institute of Canada; NS, not significant; STLI, subtotal nodal irradiation.

arms. In subsequent follow-up of PET-negative patients, 5-year PFS rates in the F group were 99.0% versus 87.1% in favor of ABVD + INRT; the U group, 92.1% versus 89.6 in favor of ABVD + INRT. In the F group, CMT resulted in a greater difference in PFS (11.9%) than in the U group (2.5%). The authors concluded that in the unfavorable group chemotherapy alone could be considered. Another objective of the H10F/U studies was to determine if intensification of therapy from ABVD therapy to escalated BEACOPP could improve outcomes for interim FDG-PET-2 positive patients. Of 1950 randomly assigned patients, 19% were PET positive. The 5-year PFS improved from 77.4% for standard ABVD + INRT to 90.6% for intensification to BEACOPPesc + NRT (hazard ratio [HR] 0.42; *P* = 0.002; see Table 21-5).

KEY POINTS



- Risk factors for early-stage HL include the presence of bulky disease, ESR, and number of nodal sites of involvement.
- More than 90% of patients with favorable disease and 85% of patients with unfavorable disease are cured with initial therapy.
- Therapeutic options for favorable early-stage HL by EORTC criteria include 3 or 4 cycles of ABVD +/– ISRT (30 Gy).
- Patients with favorable disease by GHSG HD10 criteria are eligible for 2 cycles of ABVD + 20 Gy of ISRT.
- Therapeutic options for unfavorable early-stage HL include 4 cycles of ABVD + 30 Gy of ISRT; 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD + 30 Gy of ISRT in patients fitting criteria for the GSHG HD14; or chemotherapy alone with ABVD for 4 to 6 cycles if interim PET is negative.

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Frontline therapy for advanced-stage HL

CLINICAL CASE

A 45-year-old man with a history of hypertension and asthma presented with a firm, fixed 3 to 4 cm right-sided submandibular and cervical adenopathy. Biopsy of a right axillary lymph node demonstrated large, pleomorphic lymphoma cells positive for CD15 and CD30 and negative for ALK-1, CD3, CD20, and CD45, that was consistent with cHL, NS subtype. PET and CT scans demonstrated extensive bilateral cervical, supraclavicular, axillary, mediastinal, hilar, and retroperitoneal adenopathy with standardized uptake values of 7.3 to 18.5, and small bilateral pulmonary nodules. The patient had no B symptoms, ESR was elevated at 82, and he had 6 adverse prognostic features by the International Prognostic Score (IPS), including male gender, age >45 years, white blood cells 15.5, hemoglobin 8.6 mg/dL, albumin 3.0 g/dL, and stage IV disease. Ejection fraction was normal at 55% on pretreatment multigated acquisition scan. Treatment was given with brentuximab vedotin and AVD, and he achieved a complete response to therapy.

Advanced-stage HL is generally classified as Ann Arbor stages III and IV, but clinical trials have often incorporated patients with high-risk stage II disease, such as those with B symptoms, multiple sites, and/or bulky disease. Approximately 70% to 80% of younger patients with advanced-stage HL remain disease-free at 10 years with conventional chemotherapy, in contrast to early-stage cHL, where the long-term cure exceeds 90%. Different prognostic indices are used for early- and advanced-stage disease. Prognosis in advanced-stage may be defined by the IPS (Table 21-6), originally published in 1998, including measurements of albumin, hemoglobin, sex, age older than 45 years, stage IV, and the presence of leukocytosis or lymphocytosis. Patients with an IPS ≥3 were found to have inferior treatment outcomes and were identified as potentially requiring more intensive therapy. In an updated analysis of the IPS performed by the British Columbia Cancer Agency, 5-year freedom from progression (FFP) and OS ranged from 62%-88% and 67%-98%, respectively. Controlling for all IPS factors, only age and hemoglobin level retained independent significance.

Table 21-6 International Prognostic Score in advanced-stage Hodgkin lymphoma

	5-y FFP (%)		5-y OS (%)	
No. of risk factors*	1998	2012	1998	2012
0	84	88	89	98
1	77	85	90	97
2	67	80	81	92
3	60	74	78	91
4	51	68	61	88
>5	42	70	56	73

From Hasenclever D, Diehl V, *N Engl J Med*. 1998;339:1506-1514, and Moccia AA et al, *J Clin Oncol*. 2012;30:3383-3388.

*The IPS is derived from a retrospective analysis of 5141 patients treated at 25 centers from 1983 to 1992 with advanced-stage HL. Risk factors identified in this retrospective study included age >45 years, male gender, white blood count >15,000/mm^3, Hb <10.5 g/dL, absolute lymphocyte count <600/mm^3 or <8% of white blood count, albumin <4.0 g/dL, and stage IV disease. More recent data on the value of IPS suggest that the impact might have narrowed in the modern treatment era (Moccia et al, 2012).

Initial treatment options for advanced-stage disease include ABVD/AVD, brentuximab vedotin + AVD (A + AVD), or escalated BEACOPP (Table 21-7). The randomized phase 3 study, ECHELON-1, replaces bleomycin in ABVD with the CD30 drug-antibody conjugate, brentuximab vedotin (A + AVD), challenging the role of ABVD as the standard frontline regimen in this patient population.

For patients initially treated with ABVD or BEACOPP, interim PET after 2 cycles of therapy is generally recommended and may allow for further adjustments in therapy depending on response. The negative predictive value of an interim PET scan following ABVD is relatively high, ranging from 86% to 95%, but the positive predictive value (PPV) may be as low as 44%. In contrast, the negative predictive value of escalated BEACOPP is very high, generally estimated at >95%. Table 21-8 shows a summary of randomized trials in advanced HL.

ABVD

ABVD remains a common regimen for initial treatment of advanced-stage classical Hodgkin lymphoma. ABVD is routinely followed by interim PET scanning. The largest trial to date assessing PET-directed therapy was the phase 3, randomized response adapted therapy for Hodgkin lymphoma (RATHL) study. Eligibility included patients with stage IIB to IV disease or stage IIA disease with adverse features (eg, bulky disease or at least 3 involved sites). Interim PET was performed after 2 cycles, with negativity defined as a Deauville score of 1-3. Patients with a negative PET-2 scan were randomized either to continuation of ABVD or to omission of bleomycin (AVD group) for cycles 3 through 6. The positive PET group received BEACOPP. Radiotherapy was not recommended for patients with negative findings on interim scans. In those treated with ABVD or AVD, results demonstrated that deescalation to AVD in patients with a negative PET2 was non inferior, with a 3-year PFS of 85.7% and 84.4% and OS of 97.2% and 97.6%, respectively. Additionally, respiratory adverse events were more severe in the bleomycin-containing group. The PET-positive group (n = 182) had a 74.4% rate of negative repeat PET after BEACOPP; the 3-year PFS was 67.5% and the 3-year OS was 87.8%.

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Table 21-7 Frontline chemotherapy regimens in Hodgkin lymphoma

Regimen	Drugs	Method of administration	When administered	Cycle
A + AVD	Brentuximab vedotin 1.2 mg/kg	IV	Days 1 and 15	Q 28 days
	Doxorubicin 25 mg/m^2	IV	Days 1 and 15	
	Vinblastine 6 mg/m^2	IV	Days 1 and 15	
	Dacarbazine 375 mg/m^2	IV	Days 1 and 15	
ABVD	Doxorubicin 25 mg/m^2	IV	Days 1 and 15	Q 28 days
	Bleomycin 10 units/m^2	IV	Days 1 and 15	
	Vinblastine 6 mg/m^2	IV	Days 1 and 15	
	Dacarbazine 375 mg/m^2	IV	Days 1 and 15	
BEACOPP (baseline)	Bleomycin 10 mg/m^2	IV	Day 8	Q 21 days
	Etoposide 100 mg/m^2	IV	Days 1-3	
	Doxorubicin 25 mg/m^2	IV	Days 1	
	Cyclophosphamide 650 mg/m^2	IV	Day 1	
	Vincristine 1.4 mg/m^2 (capped at 2.0 mg)	IV	Day 8	
	Procarbazine 100 mg/m^2	IV	Days 1-7	
	Prednisone 40 mg/m^2	IV	Days 1-14	
BEACOPP (escalated)	Bleomycin 10 mg/m^2	IV	Day 8	Q 21 days
	Etoposide 200 mg/m^2	IV	Days 1-3	
	Doxorubicin 35 mg/m^2	IV	Days 1	
	Cyclophosphamide 1250 mg/m^2	IV	Day 1	
	Vincristine 1.4 mg/m^2 (capped at 2.0 mg)	IV	Day 8	
	Procarbazine 100 mg/m^2	IV	Days 1-7	
	Prednisone 40 mg/m^2	IV	Days 1-14	

IV, intravenous; Q, every.

Escalation to BEACOPP in PET2-positive patients was also supported in a large phase 2 study led by the US Intergroup: with a median follow-up of 39.7 months, the 2-year PFS was 82% for PET-2-negative and 64% for PET-2-positive patients who switched to eBEACOPP, compared to the historic control of 13% PFS at 2 years in patients who continued ABVD.

Brentuximab vedotin and chemotherapy

Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate containing monomethyl auristatin E. In the multicenter, randomized, phase 3 trial (ECHELON-1) patients with stage III or IV cHL were randomized to brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A + AVD) (n = 664) versus standard ABVD (n = 670) for 6 cycles. The 2-year modified PFS rates in the A + AVD and ABVD groups were 82.1% and 77.2%, respectively, resulting in a difference of 4.9 percentage points (HR for an event of progression, death, or modified progression, 0.77; P = 0.03). This difference increased to approximately 7% difference at 3 and 5 years follow-up. The A + AVD group had more neutropenia, but the rate of febrile neutropenia was lower among patients who received primary prophylaxis with granulocyte colony-stimulating factor versus those who did not (11% versus 21%), leading to a recommendation for G-CSF prophylaxis with this regimen. Peripheral neuropathy was more common in A + AVD but was reversible in 67% of patients at 2 years. Grade 3 or higher pulmonary toxicity was rare, being reported in <1% of patients receiving A + AVD and 3% of those treated with ABVD. Modified progression-free survival was a novel endpoint, which included the use of modified progression events, defined as less-than-complete remission to frontline therapy (an end-of-treatment positron emission tomography scan score of Deauville 3-5 and the delivery of subsequent treatment). However, follow-up studies have also confirmed superiority of A + AVD using the standard PFS measure. Overall, 6 cycles of A + AVD is associated with a 7% lower combined risk of progression, death or to noncomplete response and use of subsequent anticancer therapy at 3 and 5 years compared to 6 cycles of ABVD.

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Table 21-8 Summary of randomized frontline trials in advanced-stage Hodgkin lymphoma

Trial	N	Treatment regimens	PFS/EFS	OS
ECHELON-1	1334	A + AVD ABVD	3-year PFS 83.1% 76.0% $P = 0.008$	 28 deaths 39 deaths HR = 0.73
GHSG HD18	1100	2 escBEACOPP followed by PET PET-2 negative: 2 vs. 4-6 escBEACOPP PET-2 positive: escBEACOPP + rituximab 6 escBEACOPP	5-year PFS 90.8% 92.2% 89.7% 88.1% P = NS	5-year OS 95.6% (overall) P = NS
LYSA AHL2011	823	6 escBEACOPP PET-directed: 2 escBEACOPP followed by PET PET-2 negative: 4 ABVD PET-2 positive: 4 escBEACOPP	5-year PFS 86.2% 85.7% $P = 0.7$	5-year OS 95.2% 96.4% $P = 0.43$
RATHL	1412	2 ABVD followed by PET PET negative: 4 ABVD 4 AVD PET positive: BEACOPP	3-year PFS 85.7% 84.4%, P = NS 67.5%	3-year OS 97.2% 97.6%, P = NS 87.8%
GHSG HD15	2126	 8 escBEACOPP +/− 30Gy IFRT 6 escBEACOPP +/− 30Gy IFRT 8 BEACOPP-14 +/− 30Gy IFRT	5-year FFTF 84.4% 89.3% 89.4% $P = 0.009$	5-year OS 91.9% 95.3% 94.5% $P < 0.019$
EORTC 20012	549	For patients IPS 4-7 only: 8 ABVD 4 escBEACOPP and 4 base cycles	4-year EFS 63.7% 69.3% P = NS	4-year OS 86.7% 90.3% P = NS
GITIL/FIL HD0607	786	2 ABVD followed by PET PET negative: ABVD × 4, RT No RT PET positive: escBEACOPP + RT BEACOPP + rituximab + RT	3-year PFS 87% (overall) 97% 93%, $P = 0.29$ 60% 63% 57%, $P = 0.53$	 97% (overall) 99% 89%
SWOG S0816	336	2 ABVD followed by PET PET negative: 4 ABVD PET positive: 6 escBEACOPP	5-year PFS 76% 66%	5-year OS 94%

base, baseline; LYSA, Lymphoma Study Association; NS, not significant.

However, patients older than age 60 had no difference in outcomes between the 2 treatment regimens, but with higher toxicity in A + AVD.

BEACOPP

BEACOPP is a GHSG-derived regimen that been studied in 3 major varieties: baseline BEACOPP, BEACOPP-14, and escalated BEACOPP. Escalated BEACOPP (escBEACOPP) differs from ABVD by incorporating elevated doses of etoposide, doxorubicin, and cyclophosphamide. Several randomized comparisons of these regimens have identified improved PFS with BEACOPP compared to ABVD (PFS = 65% to 70% in ABVD at 10 years, compared with 75% to 85% with escBEACOPP) but with similar OS of approximately 75% to 85% at 10 years (Table 21-9). However, a large meta-analysis comparing initial treatment with ABVD to escBEACOPP demonstrated a significant improvement in overall survival in patients who were treated with 6 cycles of escalated BEACOPP initially, with an absolute OS difference of 5% to 10% at 5 years. Improved disease control comes at the expense of increased rates of infertility, grade 4 infections, hospitalizations for neutropenia, and a slightly increased risk of secondary hematologic malignancies compared to ABVD. escBEACOPP is not recommended for patients older than 60 years. Table 21-8 presents further details.

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Table 21-9 National Comprehensive Cancer Network recommendations for monitoring and screening beyond 5 years*

Category	Recommendation
General health maintenance	Annual history and physical, blood pressure and laboratory studies (CBC with differential, chemistry panel, fasting glucose, thyroid-stimulating hormone if radiation near neck, and biannual lipids)
Vaccinations	Annual influenza and pneumococcal, *Haemophilus influenzae* type b conjugate after 5 to 7 years if treated with splenic RT or splenectomy and/or 6 months following stem cell transplantation (including hepatitis B virus, diphtheria, acellular pertussis, and tetanus; measles, mumps, rubella, and varicella live vaccines may be given for seronegative patients 2 years after transplant, if no immunosuppressive therapy for at least 6 months)
Cardiovascular	Consider cardiac stress test or echocardiogram at 10-year intervals after treatment
Carotid	Consider carotid ultrasound if neck radiation
Breast cancer	Initiate 8 to 10 years posttherapy, or age 40 years, whichever comes first, with MRI in addition to mammography for women who received irradiation to the chest and/or axilla between the ages of 10 and 30
Cervical, colorectal, endometrial, lung, prostate cancer	Per standard American Cancer Society cancer screening guidelines
Miscellaneous	Counseling for reproduction, health habits, psychosocial, and skin cancer risk

MRI, magnetic resonance imaging.

*A full treatment summary should be completed for each patient with consideration for referral to a survivorship clinic.

Given the increased toxicity with escBEACOPP, 2 large trials have looked at limiting the number of cycles. GHSG HD 15 demonstrated that 6 cycles of BEACOPP escalated were superior to 8 cycles in terms of OS and FFTF, with 5-year FFTF of 89.3% versus 85.4% for 6 and 8 cycles of escBEACOPP, respectively ($P = 0.009$). Further reduction from 6 to 8 cycles to 4 in patients achieving a negative interim PET is supported by the GHSG HD18 randomized, phase 3 trial, which showed equivalent outcomes but fewer severe infections and organ toxicities in patients treated with 4 cycles. Deescalation to ABVD is also supported by a small study of 45 patients with advanced-stage HL and an IPS score ≥3. Patients with a Complete response (CR) or Partial response (PR) following 2 initial cycles of escBEACOPP were deescalated to ABVD for 4 additional cycles. The 4-year PFS for early PET-negative and early PET-positive patients was 87% and 53%, respectively ($P = 0.01$).

NCCN guidelines include consideration of escBEACOPP for patients younger than 60 years old with advanced-stage HL and an IPS score ≥3. It should be noted that this regimen is associated with mandatory G-CSF support, aggressive prophylactic antiemetics, dose-adaptation upon toxicity, and potential hospitalization during the first course for higher-risk patients.

Radiation therapy or autologous transplantation as consolidation in stage III-IV HL

Several studies have examined the role of consolidative RT in patients with advanced-stage HL, and, to date, no study has demonstrated a clear OS advantage with combined modality therapy in patients responding to chemotherapy alone. However, 2 studies have shown that PET-adapted radiation in patients with residual PET-positive masses in advanced-stage cHL is feasible and results in favorable long-term outcomes following ABVD or escalated BEACOPP.

Two studies assessed PET-directed radiation following a BEACOPP regimen. The GHSG HD15 trial evaluated PET-CTs in patients who had residual PET-positive disease >2.5 cm after 6 to 8 cycles of BEACOPP. Patients who were PET-positive received 30 Gy RT consolidation. PFS at 48 months was 93% in PET-negative patients and 86% in PET-positive patients who received radiation. Although the irradiation of PET-positive patients with residual mass was not performed in a randomized fashion and there was no biopsy-proven active disease, the high tumor control rate suggests that radiating PET-positive disease after BEACOPP is a feasible approach. The GHSG HD12 trial randomized responding patients after BEACOPP with stage IIB-IV HL and with bulky or residual tumor on CT imaging either to additional consolidative RT or to no RT. Five-year FFTF was 87% in those patients who did not receive RT compared with 90% in the RT arm ($P = 0.08$). However, high-risk patients received RT irrespective of their group.

The omission of radiation in patients with a negative end-of-treatment PET following ABVD is supported by a randomized trial. In the GITIL, Gruppo Italiano Terapie Innovative nei Linfomi/Fondazione Italiana Linfomi (GITIL/FIL) HD 0607 trial, 739 patients with advanced-stage HL patients with a CR at the end of therapy were randomized to observation or IFRT. There was no

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difference in 5-year OS ($P = 0.07$) or event-free survival (EFS) ($P = 0.35$) in the RT group compared with the observation group.

Several trials have also examined the role of frontline consolidative autologous transplantation to improve outcomes in patients with high-risk, advanced-stage HL. To date, none have demonstrated a clear role for transplantation.

Novel frontline chemotherapy combinations

Other frontline combinations incorporating checkpoint blockade and brentuximab vedotin have been evaluated.

Cohort D of the CheckMate 205 study evaluated the combination of nivolumab and AVD preceded by a single-agent nivolumab lead-in among patients with stage 3-4 cHL or stage 2 with risk factors. There were some toxic events with 3 patients discontinuing for toxicity prior to completion, 1 for progression, and 3 for other events, but treatment was efficacious with a 21-month PFS of 83%.

Similarly, pembrolizumab was studied in a sequential fashion in small phase 2 study of early-stage unfavorable and advanced-stage cHL resulting in 100% complete response, PFS, and survival at a median follow-up of approximately 2 years. Given the efficacy of checkpoint blockade in the frontline setting, it has been chosen as the challenger to A + AVD in a phase 3 trial (NCT03907488) of newly diagnosed cHL in adults and children.

Likewise, brentuximab added to a BEACOPP-like in a phase 2 trial of advanced-stage cHL. The BrECADD regimen (brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, and dexamethasone) was associated with a more favorable toxicity profile and was, therefore, selected to challenge the standard escBEACOPP regimen for the treatment of advanced cHL in the phase 3 HD21 study by the GHSG (NCT02661503).

Future directions and upcoming studies in frontline therapy for HL

Given the approval and efficacy of 3 new targeted drugs approved for cHL in the past several years, additional approaches adding immunotherapy and brentuximab in the frontline are ongoing. A multicenter, phase 2 trial will assess pembrolizumab in children and young adults with newly diagnosed cHL with slow early response to frontline chemotherapy (KEYNOTE 667). A sequential study of avelumab followed by AVD in stage 2 with risk factors, and stage 3-4 cHL (NCT03617666) is ongoing. Novel biomarkers of response with ongoing evaluation include PD ligand expression on HRS cells, the tumor microenvironment, and peripheral blood, as well as soluble PD-L1 and alterations in chromosome 9p24.1.

KEY POINTS

- Therapeutic options for advanced-stage HL include A + AVD, PET-directed ABVD, and escalated BEACOPP for 4 to 6 cycles.
- The ECHELON-1 study of brentuximab vedotin and AVD resulted in an absolute 7.1% improvement in PFS at 3 years compared with ABVD in patients with stage III/IV classical HL.
- Escalated BEACOPP is associated with superior PFS compared with ABVD in patients with advanced-stage HL and may be considered as frontline therapy for patients younger than 60 years with high-risk disease; the benefit with respect to OS remains unclear.
- Deescalation of ABVD to AVD for PET2 negative patients is non inferior to ABVD alone (RATHL study).
- Escalation from ABVD to BEACOPP for PET-2-positive patients results in superior outcomes compared with historic controls that continued ABVD therapy.
- PET scans may be used to guide consolidative RT following in patients with advanced-stage HL treated with ABVD or BEACOPP with residual disease on end-of-treatment scans.

HL in older patients

Older patients with HL are defined as aged 60 years or older and constitute between 15% and 25% of all HL patients in population-based studies. Three-year OS rates are approximately 55% to 70%, and there is no standard of care in this population.

Older patients have higher complication rates from chemotherapy and up to 1/3 may develop BLT in comparison to <2% to 3% for younger patients. The risk of death from BLT is also higher, with up to 25% mortality. In a GHSG analysis, elimination of bleomycin among older patients with early favorable HL resulted in decreased local control; however, OS rates exceeded 98%. Altogether, these data suggest that an upfront regimen of AVD may be considered, particularly in patients at high risk for BLT. Alternatively, bleomycin may be safely omitted after 2 cycles in those achieving an interim complete response without compromising efficacy as demonstrated in the phase 3 trial of PET-adapted therapy by the EORTC. Older patients with favorable-risk disease received either 2 cycles of ABVD or AVD each followed by IFRT compared with 4 cycles of ABVD. Grade 3/4 events and BLT were higher in patients receiving 4 cycles of therapy (65% overall). In patients with unfavorable or advanced-stage disease, the RATHL demonstrated no differents with de-escalation of ABVD to AVD in cycles 3 to 6 in those with a negative interim PET scan after 2 cycles of ABVD.

Frontline trials using novel agents in older patients include a trial of brentuximab monotherapy, which

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demonstrated an objective overall response rate (ORR) of 92%; however, the risk of relapse was high. Combination with dacarbazine retained response (ORR 100%) and improved PFS, however bendamustine combination was associated with a higher risk of death. A multicenter phase 2 study in 48 older HL patients used initial single-agent brentuximab vedotin for 2 cycles, followed by standard AVD for 6 cycles with subsequent consolidative brentuximab vedotin for 4 cycles. The reported ORR and CR rates were 95% and 90%, respectively, and the 3-year PFS and OS rates were 84% and 93%, respectively, despite the majority of patients not receiving the full course of consolidative BV following AVD. Furthermore, geriatric-based measures (eg, comorbidity score and loss of instrumental activities of daily living) were associated with patient outcome. These results are among the best reported in this patient population. A less intense frontline therapy combining brentuximab vedotin and nivolumab was also recently evaluated in older patients. This study enrolled 46 patients with a median age of 71.5. Patients were treated with both drugs every 21 days for 8 cycles. The study was closed early for not meeting the predefined interim efficacy criteria, but results of the preliminary data show an ORR of 61% with 48% achieving a CR. Although the trial did not meet its prespecified activity criteria, it showed the combination is an effective option in older patients with comorbidities.

Therapy for relapsed or refractory HL

CLINICAL CASE

A 32-year-old man presented in with stage 3 cHL involving with disease above and below the diaphragm and extranodal disease involving the liver and spleen. He received ABVD with a negative PET scan after cycles 2 and deescalated therapy to AVD for 4 additional cycles. End-of-treatment imaging showed a CR. A CT scan 8 months later demonstrated a new liver lesion and biopsy confirmed HL. He received 3 cycles of ICE (ifosfamide, carboplatin, and etoposide); achieved a second CR on PET; and underwent autologous stem cell transplantation followed by 1 year of brentuximab vedotin maintenance therapy. One year following transplantation, he developed progressive mediastinal and intra-abdominal adenopathy; biopsy of a retroperitoneal lymph node by endoscopic ultrasound confirmed recurrent HL. He then received pembrolizumab therapy every 3 weeks, which was complicated by a skin rash treated with topical corticosteroids, and hypothyroidism treated with thyroid replacement therapy. He has 1 brother who is not an HLA match, but he does have several donor options through the National Marrow Donor Program registry.

Salvage therapy for second-line therapy

More than 80% of patients with HL achieve complete remission with initial therapy; however, up to 40% of patients with advanced-stage disease and 10% to 15% with limited-stage disease may relapse and require additional treatment. Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) remains the standard of care for patients with relapsed or refractory HL. High-dose chemotherapy and ASCT cure more than 50% of patients, with long-term PFS in 60% to 70% of patients presenting with relapsed disease and 30% of those with primary refractory disease. The optimal initial salvage regimen is not yet known, but current guidelines recommend use of multiagent chemotherapy followed by autologous transplantation in eligible patients. In terms of salvage chemotherapy regimens, commonly used options include ICE, GVD (gemcitabine, vinorelbine, and liposomal doxorubicin), DHAP (dexamethasone, cytarabine, and cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), IGEV (ifosfamide, gemcitabine, vinorelbine, and prednisolone), and BeGEV (bendamustine, gemcitabine, etoposide, and vinblastine), with responses ranging from 70% to 90%.

Other novel second-line treatments

Other novel therapies and combinations approved in the second-line setting include pembrolizumab GVD, brentuximab, pembrolizumab, brentuximab plus nivolumab, brentuximab plus bendamustine.

With increased use of brentuximab vedotin in the frontline setting for cHL, the pembrolizumab and GVD regimen was developed for transplant eligible patients with relapsed/refractory cHL after frontline treatment. In a phase 2 study of 38 patients, pembrolizumab plus GVD was associated with a CR rate of 95% and favorable toxicity profile, with 36/38 proceeding to transplant. All 36 transplanted patients remained in remission at a median follow-up of 13.5 months posttransplant. Overall, this regimen has proved to be a safe an effective outpatient salvage regiment to bridged patients with relapsed/refractory cHL to ASCT.

Other combinations have included brentuximab vedotin plus nivolumab, which was evaluated in 2 studies of relapsed cHL In the first (NCT02572167), patients in first relapse were treated 4 cycles of combination therapy every 2 weeks. Approximately 75% went on to ASCT following doublet therapy. At 2 years, the estimated 2-year PFS was 78% overall, and 91% in those who underwent ASCT. The estimated 2-year OS was 94% in all treated patients. Immune-related adverse events were

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common, but only 14% of patients required systemic steroids. In the second trial (NCT01896999), 3 brentuximab combinations were assessed: brentuximab vedotin combined with ipilimumab, nivolumab, or both (triplet therapy group). Treatment was longer in this trial, with a maximum duration of therapy of 1 year for brentuximab, 2 years for nivolumab, and 1 year in the ipilimumab group. Similarly, the ORR was high at 89% with brentuximab/nivolumab, and 82% in the triplet therapy group, with most patients achieving a CR. The 2 most active regimens, brentuximab vedotin/nivolumab and the triplet therapy are being compared in a randomized phase 2 trial (NCT01896999). Based on these results brentuximab and nivolumab are listed in the NCCN as therapy options in second-line therapy for cHL. Lastly, brentuximab and bendamustine were efficacious and did not appear to hinder the ability to collect stem cells. PFS at 3 years was 60.3% for those undergoing ASCT versus. 40.4% for those who did not.

Autologous stem cell transplantation

Despite the promising efficacy of novel agents, ASCT is still recommended for eligible patients in first relapse following salvage therapy. Data supporting this recommendation are based on 2 prospective randomized trials. The British National Lymphoma Group randomized 40 patients with relapsed disease either to BCNU, etoposide, cytarabine, melphalan (BEAM) followed by ASCT or to mini-BEAM alone; high-dose chemotherapy and ASCT demonstrated a significant PFS benefit ($P = 0.005$). A larger trial of 161 chemosensitive patients randomized to 2 cycles of Dexa-BEAM and ASCT or 2 more cycles of Dexa-BEAM demonstrated a 3-year FFTF of 55% with transplantation compared with 34% without transplantation. Neither trial, however, demonstrated an OS benefit, perhaps because of limited follow-up or small patient numbers.

Chemoresistance to second-line therapies further predicts worse survival; OS was 39% at 5 years in patients with refractory disease to initial induction therapy compared to 67% in chemosensitive patients in one study, but the approval of targeted agents has improved outcomes in these patients. Additional features identifying patients at high risk for relapse posttransplantation include failure to attain PET negativity immediately prior to transplantation, short initial remission duration (<1 year), and extranodal disease.

A number of studies have demonstrated the prognostic value of PET/CT in this setting. It is reasonable to recommend 2 or 3 cycles of salvage chemotherapy, confirm response of disease by PET/CT, and then proceed with ASCT in responding patients. For those with progressive disease on PET/CT scans, alternative salvage regimens with novel agents should be considered, and, if patients respond, ASCT is still advocated.

Posttransplant maintenance

A prospective phase 3 clinical trial, AETHERA, randomized a total of 322 cHL patients after treatment with high-dose chemotherapy and ASCT between consolidation treatment with brentuximab vedotin or placebo. Patients were included if they had at least 1 of the following risk factors for progression after ASCT: primary refractory HL, relapsed HL with initial remission duration <12 months, or extranodal involvement at the start of pretransplant at salvage chemotherapy. Treatment was given at 1.8 mg/kg in 3-week intervals for up to 16 cycles. The hazard ratio of this trial was 0.57 ($P = 0.001$) with a median PFS in the brentuximab vedotin arm of 42.9 months and 24.1 months in the group treated with placebo. Thus, consolidation treatment with brentuximab vedotin has been established as a treatment option for patients with higher risk of relapse following ASCT. Posttransplant pembrolizumab has also been studied in this setting in a phase 2 trial with favorable results but is not recommended as standard of care at this time.

Therapeutic options for patients relapsing after autologous stem cell transplantation or not eligible for transplantation

Historically, patients who relapsed after ASCT had poor outcomes, with a median survival of 1 to 2 years. However, the routine use of novel targeted therapies has improved outcomes in these patients. These therapeutic agents include the CD30 antibody-drug conjugate brentuximab vedotin as well as the PD-1 inhibitors pembrolizumab and nivolumab. These agents have largely replaced salvage chemotherapy as the preferred treatment in these settings because of their efficacy and tolerability. A retrospective analysis demonstrated that treatment with these novel targeted agents is associated with significant improvement in OS compared to historic therapy with chemotherapy alone (median survival of 85.6 months versus 17.1 months, $P = 0.015$). Other factors that increase likelihood of survival at relapse include post-ASCT radiation therapy (34.1 versus 17.0 months; $P = 0.015$).

Anti–PD-1 therapy

Pembrolizumab is a highly selective humanized IgG4-κ isotype antibody that is also directed against PD-1, and it demonstrated impressive response rates in phase 1 and 2 clinical trials of relapsed cHL. The phase 2 study

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KEYNOTE-087 used a flat dose of 200 mg every 3 weeks. The ORR was 69.0% and the CR rate was 22.4%, which improved to 71.9% ORR and 27.6% CR rate at 5 years. There were some with durable response, with 31 patients maintaining a response of ≥6 months. On 14 October 2020, the FDA expanded the approval for pembrolizumab for adult patients with relapsed or refractory cHL and pediatric patients with refractory or cHL that has relapsed after 2 or more lines of therapy based on KEYNOTE-204 (NCT02684292) a phase 3 randomized study comparing pembrolizumab to brentuximab vedotin in relapsed/refractory cHL after at least 1 multiagent regimen. PFS was longer in the pembrolizumab arm at 13.2 months compared to 8.3 months with brentuximab ($P = 0.0027$). Serious adverse events included pneumonitis, pneumonia, myocarditis, kidney injury, and febrile neutropenia, with 38% of patients experiencing adverse events requiring systemic corticosteroids including 11% with pneumonitis. The recommended dose is either 200 mg every 3 weeks, or 400 mg every 6 weeks for adults for up to 2 years.

Nivolumab is a high-affinity, fully human IgG4 (S228P) monoclonal antibody directed against PD-1. It is approved for patients with cHL who have relapsed or progressed after ASCT and posttransplant brentuximab vedotin treatment. The phase 2 clinical trial, CheckMate 205, assessed patient who had failed prior ASCT and had either relapsed or failed brentuximab vedotin. Overall, 66% of patients achieved a response. The recommended dose schedule is 240 mg every 2 weeks. Additionally, 44 patients in CheckMate205 subsequently proceeded to allogeneic SCT. The 6-month cumulative incidence of treatment-related mortality (TRM) was 13%, and 7% had disease progression. The cumulative 6-month incidence of grade 3 or 4 acute graft-versus-host disease (GVHD) was 20%, and 15% had chronic GVHD. Univariate analysis did not identify associations between time from last dose of nivolumab to allogeneic SCT and TRM. These data appear grossly comparable with historical relapsed/refractory HL cohorts receiving allografts without preceding PD-1 blockade. The 6-month PFS and OS estimates were 82% and 87%, respectively. However, PD-1 therapy after allogeneic transplantation may be associated with higher rates of severe GVHD (see "Allogeneic transplantation").

Brentuximab vedotin

The FDA approved BV in 2011, a novel anti-CD30 drug-antibody conjugate for the treatment of patients with relapsed or refractory HL after previous ASCT. BV is composed of a CD30 antibody conjugated by a plasma-stable link to the antimicrotubule agent, monomethyl auristatin E. In a pivotal phase 2 study with 102 relapsed (29%) or refractory (71%) cHL patients who had received a median of 3.5 prior therapies (range 1-13), the ORR was 75%, with a 33% achieving CR. OS was 40.5 months and grade 3-4 toxicities consisted of sensory neuropathy (8%), neutropenia (20%), and thrombocytopenia (8%). BV may be administered for up to 16 cycles, with dose reductions or delays, if needed, for myelosuppression or neuropathy.

Radiation

Radiotherapy should also be considered in the setting of relapsed HL in highly selected patients with limited-stage disease at relapse who may not be eligible for ASCT because of age and comorbid conditions. In a retrospective analysis of salvage RT used in 100 patients at first treatment failure, 5-year FFTF and OS were 28% and 51%, respectively, with RT alone. For younger patients with relapsed HL, because of potential risks of second malignancies within the radiation field and improved survival with ASCT, RT alone is not recommended at first relapse. IFRT, however, should be considered in these patients as consolidation post-ASCT to bulky, nonirradiated sites or to sites of relapsed limited-stage disease in previously nonirradiated fields.

Chemotherapy

A number of single-agent regimens are used in the palliative setting and include vinblastine, etoposide, gemcitabine, and vinorelbine. With vinblastine (4 to 6 mg/m^2 weekly or every 2 weeks until disease progression or toxicity), response rates as high as 59% and median EFS of 14 months have been reported. Gemcitabine and vinorelbine both have single-agent activity in 39% to 50% of patients. The histone deacetylase inhibitor panobinostat also has activity in this population, including multiply relapsed disease; however, histone deacetylase inhibitors (HDAC) inhibitors are not FDA approved for HL. Selected patients with nonbulky lymphadenopathy and no organ involvement who are otherwise asymptomatic also could be observed in this setting.

Allogeneic transplantation

Allogeneic transplantation has been used for patients with relapsed HL after prior ASCT, though the presence of a graft-versus-HL effect remains controversial. Most trials of allogeneic SCT (alloSCT) in HL demonstrate 2-year PFS rates of 30% and OS of 35% to 60%. Overall, for selected patients with available donors who are at least a good PR, reduced-intensity allogeneic SCT is an option after prior ASCT and may lead to prolonged disease-free survival (DFS) in 18% to 32% of patients.

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The widespread use of immunotherapy and, in particular, PD-1 inhibitors in the peritransplantation period have demonstrated notable interaction on immunologic response, recovery, and posttransplantation treatment outcomes. A multicenter retrospective analysis of 209 cHL patients who underwent alloHCT after PD-1 blockade showed a low rate of nonrelapse mortality and relapse (14 and 18%, respectively at 2 years). At 2-years, nearly half of patients were free of relapse and GVHD. PFS was 69%, and OS was 82%. The 180-day cumulative incidence of grade 3 or 4 acute GVHD was 15%, and chronic GVHD was 34%. Longer interval from PD-1 to alloHCT was associated with less frequent severe acute GVHD. Notably, posttransplant cyclophosphamide (PTCy)-based GVHD prophylaxis was associated with significant improvements in PFS and GVHD and Relapse-free survival. Caution should be exercised when using PD-1 inhibitors at relapse after allogeneic SCT for possible flare of GVHD and other immune-related toxicities, but these data suggest PTCy-based GVHD prophylaxis may be considered the optimal transplantation strategy for this patient population.

Other novel therapies

Several additional novel treatments are being investigated for patients who are ineligible for or who have relapsed following transplantation. Several other combinations with PD-1 therapies are ongoing, including pembrolizumab with radiation therapy (NCT0317991), pembrolizumab and lenalidomide (NCT02875067), pembrolizumab and ibrutinib (NCT02950220). A provocative study combining pembrolizumab with GVD chemotherapy showed 94% CR rate with 27/34 undergoing ASCT and all patients in continuous remission with a median follow-up of 9 months posttransplant. Lenalidomide is an immunomodulatory agent that has demonstrated activity in several hematologic malignancies, including HL. The largest trial of single-agent lenalidomide (n = 38) demonstrated an ORR of 19% and CR rate of 3%. Lenalidomide combined with bendamustine (Leben combination) resulted in an ORR of 75% and a CR rate of 44%.

Lastly, cellular therapies including Car-T therapies have demonstrated early promise. CD30 directed Car-T therapy was assessed in 31 patients with relapsed or refractory Hodgkin lymphoma in 2 parallel phase I/II studies (NCT02690545 and NCT02917083) after lymphodepletion with either bendamustine alone, bendamustine and fludarabine, or cyclophosphamide and fludarabine. Results showed grade 1 only cytokine release syndrome in 10 patients, no episodes of neurotoxicity, and a response up to 72% in those receiving fludarabine-based lymphodepletion. 1-year PFS was 36% and OS of 94%. Lastly, AFM-13 is a CD30 and NK-cell targeting bispecific antibody with early data showing some efficacy in relapsed Hodgkin lymphoma when combined with pembrolizumab with an ORR of 83%.

KEY POINTS

- Fit older HL patients should be considered for sequential brentuximab vedotin therapy given before and after standard AVD chemotherapy; less-fit older patients not amenable to standard combination chemotherapy may be considered for treatment with brentuximab vedotin with dacarbazine.
- Salvage therapy followed by autologous transplantation offers superior PFS compared with chemotherapy alone in patients with relapsed, chemosensitive HL.
- Posttransplantation brentuximab vedotin is recommended for patients with a high risk of posttransplantation relapse based on the phase 3 AETHERA trial.
- Brentuximab vedotin leads to overall response rates of 75% in patients with relapsed HL following autologous transplantation.
- Nivolumab and pembrolizumab are anti–PD-1 antibodies approved for patients with relapsed/refractory Hodgkin lymphoma with ORR of approximately 70%.
- Pembrolizumab is associated with improved PFS compared to brentuximab vedotin in patients with one prior line of therapy based on the KEYNOTE-087 randomized clinical trial.

Nodular lymphocyte-predominant HL

CLINICAL CASE

A 19-year-old college student and lacrosse player presented with left-sided cervical adenopathy and a large parotid mass of 6 cm, initially thought to be secondary to acute infectious mononucleosis. The mass failed to improve despite 6 months of intermittent steroids and antibiotics, and subsequent biopsy demonstrated atypical large cells with large nuclei that were CD20 and CD45 positive and PAX-5, BCL-2, CD15, and CD30 negative, consistent with NLPHL. CTs of the C/A/P demonstrated bilateral cervical adenopathy but no other sites of disease; bone marrow biopsy was negative.

Considered the "nonclassical" type of HL, NLPHL is an uncommon subtype of HL, representing about 5% of cases. It has unique clinical and pathologic features

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distinguishing it from cHL. Unlike cHL, the cells are $CD20^+$ and $CD30^-$. They are also strongly positive for OCT2, which is helpful in differentiating this type of lymphoma from cHL. Because of the rare occurrence of this malignancy, presentation, treatment, and patient outcomes are not well described, but many studies show it has mainly an indolent course with a favorable prognosis. In a retrospective analysis of 8298 patients enrolled on clinical trials for HL through the GHSG, 394 patients had NLPHL. In this series, the median age at diagnosis was 37 years, 75% of patients were male, and 79% had early-stage disease. The presence of B symptoms or bulky disease is unusual and is observed in <10% of patients. Unlike cHL, patients with NLPHL typically have peripheral adenopathy (axillary or inguinal) at diagnosis rather than central or mediastinal involvement; nodal involvement is not contiguous, and extranodal involvement is uncommon.

An association exists with this subtype of lymphoma and a benign condition, progressive transformation of germinal centers, as well as with Non-Hodgkin lymphoma (NHL), particularly T-cell–rich B-cell lymphoma and diffuse large B-cell lymphoma. Progressive transformation of germinal centers is described as lymph nodes with large, well-defined nodules with an excess of B cells or germinal centers overrun by lymphocytes. Progressive transformation of germinal centers may be observed before, simultaneously with, or following a diagnosis of NLPHL. This entity is thought to be a benign condition, but, because it occurs concurrently or following a diagnosis of NLPHL, biopsy of recurrent adenopathy always is required with this disease to confirm relapse.

Likewise, T-cell-rich B-cell lymphoma can occur simultaneously or in succession and may be confused with NLPHL. Because ~5% to 10% of patients with NLPHL eventually develop NHL, biopsy of recurrent lymph nodes is necessary to determine optimal therapy at relapse. Late relapses >1 year after therapy are observed more commonly in patients with NLPHL (7.4%) compared with patients with cHL (4.7%).

No standard frontline or relapsed therapy exists for NLPHL, although a number of options are available with excellent outcomes. Adverse prognostic factors in NLPHL include advanced-stage disease, age >45 years, and spleen, liver, or bone involvement. One study showed that splenic involvement was associated with an inferior 10-year time to progression (TTP) in NLPHL (48% versus 71%; $P = 0.049$) as well as an increased cumulative incidence of secondary aggressive lymphoma ($P = 0.014$).

For early-stage NLPHL, IFRT alone is recommended, especially for patients with peripherally located stage IA disease. Two small retrospective studies of limited-stage NLPHL, with a total of 245 patients, found no benefit of combined modality therapy over radiation alone. In contrast, one retrospective comparison of 32 patients treated with RT alone versus 56 patients receiving CMT with ABVD for 2 cycles and RT demonstrated improved PFS survival (65% versus 91%, $P = 0.0024$) with CMT. Therefore, most series support favorable outcomes with RT alone in early-stage IA NLPHL.

Chemotherapy alone may be used for nonstage IA patients or for those with very high risk of late complications of RT because of the field size of RT required. Cyclophosphamide, vinblastine, and prednisolone (CVP) or single-agent rituximab may also be considered with response rates of 100% but a slightly shorter PFS compared to radiation. However, these early-stage patients who relapse after chemotherapy can be effectively salvaged with additional chemotherapy and RT, and such an approach may reduce the rates of second malignancies. Because of the risks of second malignancies and the excellent long-term outcomes observed in patients with NLPHL, observation is also an option in select patients. A retrospective study looking at 163 patients with NLPHL showed a slight decrease in PFS in patients on active surveillance but no difference in second PFS (PFS2) or OS when compared to patients who received treatment with RT, CMT, chemotherapy, or rituximab alone (PFS 77% versus 87%, PFS2 95% versus 97%, and OS 100% versus 98%, respectively). After a median follow-up of 69 months, only 10 of the 37 patients on active surveillance developed disease progression.

In the advanced-stage setting, chemotherapy options include 6 cycles of ABVD or BEACOPP, or alkylator regimens (CVP or cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)). Rituximab may be given alone as a single agent or in combination with chemotherapy. All these strategies result in response rates nearing 100%. Advani et al. reported data using single-agent rituximab induction weekly for 4 weeks followed by maintenance rituximab once every 6 months for 2 years for previously treated or newly diagnosed NLPHL. At median follow-up of 9.8 years, the median OS was not reached. Of patients who experienced relapse, 39% of NLPHLs had transformed to an aggressive B-cell lymphoma. Rituximab-CHOP was associated with estimated 5- and 10-year PFS rates of 88.5% and 59.3%, respectively, in NLPHL. With a median follow-up of 6.7 years, no patient treated with R-CHOP experienced transformation. These regimens frequently are used as frontline or salvage therapy for stage III-IV NLPHL.

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KEY POINTS

- NLPHL is a nonclassical type of HL with a different phenotype and disease course compared to classical HL.
- It can be associated with progressive transformation of germinal centers (a benign condition) and also transformation to diffuse large B-cell or T-cell-rich B-cell NHL; therefore, biopsy at relapse is necessary.
- Unlike HL, NLPHL is associated with noncontiguous nodal spread and late relapses.
- No standard therapy exists for NLPHL; IFRT is used for stage IA disease, CMT or observation is used for other early-stage disease, combination chemotherapy with rituximab (including R-CHOP) is used for advanced-stage disease, and single-agent rituximab is used in the relapsed setting.

Follow-up of patients with HL

CLINICAL CASE

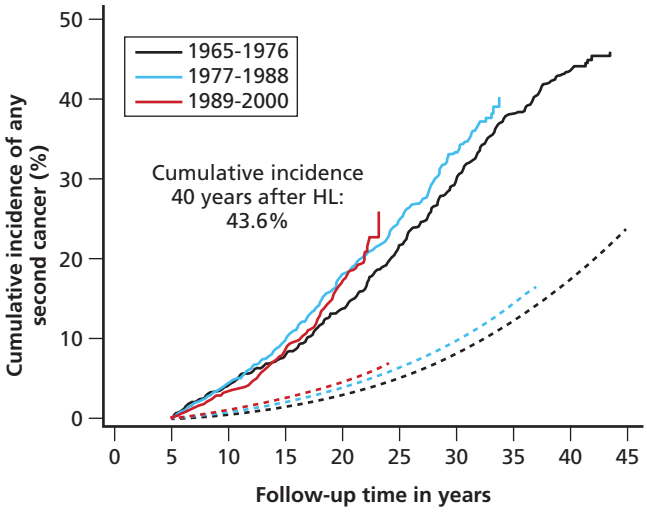
An 18-year-old nonsmoking man with no history of cardiac disease, diabetes, or elevated cholesterol presented with bulky stage IIB cHL involving the mediastinum and bilateral supraclavicular nodes. He received 6 cycles of ABVD, followed by mantle-field irradiation. He was followed every 6 months with CT scans for 2 years and then annually with CT scans until year 5 with no recurrence. After his fifth year, he relocated for a new job opportunity and was followed only as needed by a primary care physician. Approximately 15 years after diagnosis, at the age of 33, he acutely developed nausea and chest discomfort and was seen in a local emergency room. Because of lack of cardiac risk factors and initially normal electrocardiogram and troponin, he was admitted to a nonteaching service for observation with the thought that this was gastrointestinal discomfort. Subsequent troponin levels continued to rise, and the patient was urgently taken to cardiac catheterization, where he was found to have a 90% occluded left anterior descending artery.

Secondary, late therapy-related effects in HL survivors include hypothyroidism, fertility issues, secondary cancers, and cardiovascular disease. The risks of second malignancies and cardiovascular disease continue 40 years after diagnosis. Therefore, monitoring of late complications is a lifelong endeavor for HL survivors. Follow-up of patients with HL must address both the risk of relapse as well as potential late complications of therapy. The likelihood of HL recurrence declines sharply after 3 years, whereas the incidence of second malignancies and cardiovascular disease continually increased beginning 10 to 15 years from the start of treatment and continuing beyond 40 years after treatment. Within the first 5 years after diagnosis, patients should be monitored for HL recurrence with history and symptom-directed evaluation, physical examinations, and laboratory testing (CBC, platelets, chemistries, and ESR if elevated at initial diagnosis) every 3 to 6 months for the first 2 years and every 6 to 12 months during years 3 to 5.

Several studies have demonstrated no survival benefit with routine CT surveillance in patients achieving a CR at the end of therapy. Follow-up PET/CTs demonstrate a high false-positive rate, with an overall PPV of only 28%, limiting its utility as a follow-up tool for HL. Therefore, with the low risk for relapse in HL and no demonstrated survival benefit with routine surveillance imaging, follow-up should consist of history and physical examination with only symptom-directed imaging during the first 5 years after HL diagnosis. At most, CT scanning every 6 months for a maximum of 2 years after original diagnosis may be considered for surveillance.

In a meta-analysis, second cancers were more commonly encountered in patients receiving radiation-containing treatment compared with chemotherapy alone, with no significant decreases in the second malignancy rate observed with more modern radiation techniques so far (Figure 21-5). Therefore, any patient receiving previous RT should

Figure 21-5 Cumulative incidence of solid malignancy after HL according to calendar period of treatment. Adapted from van Leeuwen FE, Ng AK, *Hematology (Am Soc Hematol Educ Program)*. 2016;2016:323-330, with permission from the publisher.



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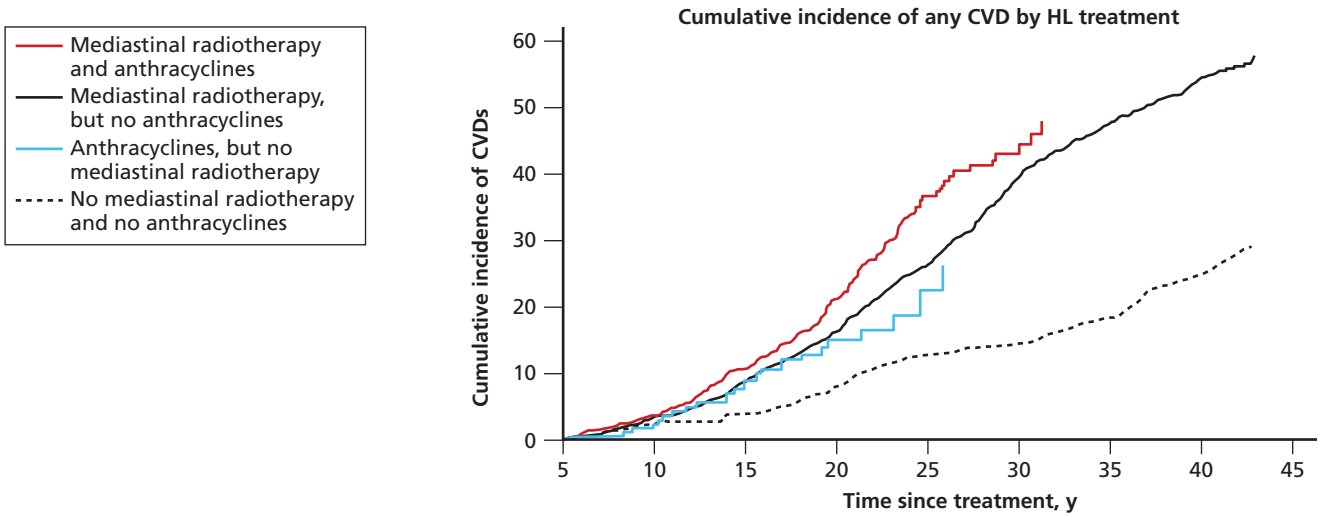

No. at risk

Mediastinal radiotherapy and anthracyclines	604	492	364	180	46	14	1	0
Mediastinal radiotherapy, but no anthracyclines	1,448	1,269	1,097	848	552	273	119	30
Anthracyclines, but no mediastinal radiotherapy	169	139	105	59	13	6	1	0
No mediastinal radiotherapy and no anthracyclines	302	270	249	158	158	110	55	16

No. at risk

Mediastinal radiotherapy and anthracyclines	22	39	47	39	9	2	0
Mediastinal radiotherapy, but no anthracyclines	48	75	102	119	123	58	32
Anthracyclines, but no mediastinal radiotherapy	3	10	8	3	1	0	0
No mediastinal radiotherapy and no anthracyclines	6	5	11	11	3	5	5

Figure 21-6 Cumulative incidence of cardiovascular disease after HL according to treatment, with death from any cause as a competing risk. Adapted from van Leeuwen FE, Ng AK, *Hematology (Am Soc Hematol Educ Program).* 2016;2016:323-330, with permission from the publisher.

be monitored for a second malignancy and cardiovascular disease (Table 21-9). The risk of secondary breast cancers is associated with young age at the time of radiation; women younger than 30 years are particularly at risk. Lung cancer risk is increased in patients receiving mediastinal radiation, particularly if they have a smoking history, and chest imaging annually should be considered for these patients at greatest risk. Secondary myelodysplastic syndrome and leukemia affect up to 1% of patients receiving ABVD and have been observed in up to 3% of patients treated with 8 cycles of escalated BEACOPP. Cardiovascular disease (CVD), including increased risk of coronary artery disease and valvular disease, also is observed in HL survivors, particularly after mediastinal radiation or anthracycline-based chemotherapy, starting about 5 years after treatment (Figure 21-6). Although optimal screening strategies are unclear, monitoring and aggressive management of cardiovascular risk factors, including smoking, hypertension, diabetes, and hyperlipidemia, is recommended with consideration of a baseline stress test or echocardiogram (Table 21-9).

Other late toxicities associated with RT include hypothyroidism, which can occur in up to 50% of patients, and radiation pneumonitis or lung fibrosis (3% to 10% of patients). Annual thyroid function tests are recommended for patients with radiation to the neck or upper mediastinum, and evaluation for pulmonary fibrosis should be considered in symptomatic patients.

With respect to fertility, patients treated with BEACOPP have a high risk of infertility depending on the age at treatment and the number of cycles received. All patients receiving chemotherapy should be counseled about this risk and referred for sperm banking or reproductive endocrinology evaluation. ABVD does not appear to significantly affect female fertility. Several large studies by the GHSG demonstrated preserved gonadal function, return of menses following chemotherapy, and equal numbers of pregnancies in female patients treated with ABVD compared to population-based controls.

Anthracycline-related cardiotoxicity in the absence of mediastinal RT is rare in this patient population because the total cumulative dose of doxorubicin administered is 300 mg/m^2 or less. An evaluation of left-ventricular function is typically obtained before the initiation of chemotherapy, although asymptomatic cardiac dysfunction is uncommon in this patient population, especially for younger patients. Additionally, there is an increased risk of

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myocardial infarction (MI) for 25 years after treatment with anthracyclines (standardized mortality ratio for MI of 7.8 with ABVD alone; and 12.1 for ABVD and RT). Aggressive management of other cardiac risk factors is recommended.

In addition to these risks, patients who undergo ASCT for relapsed disease should be monitored for risks of secondary leukemia, other secondary malignancies, hypogonadism and its complications, including declines in bone mineral density; these patients also should be considered for revaccination. In addition, patients typically experience hypogonadism posttransplantation, and monitoring for consequences of hormonal deficiency is recommended, including monitoring for bone mineral density reduction using dual energy x-ray absorptiometry (dexa) scanning.

Immunity typically wanes post–autologous transplantation, and it is recommended that patients receive pneumococcal, tetanus, *Haemophilus influenzae* type b, hepatitis B, and annual influenza vaccinations. Measles, mumps, and rubella and varicella vaccinations can be considered in immunocompetent patients no sooner than 24 months posttransplantation (Table 21-9).

KEY POINTS

- ABVD does not significantly impact fertility, whereas escalated BEACOPP is expected to reduce fertility in direct proportion to the number of cycles received.
- Treatment summaries should be completed for each patient and consideration given to referral to a survivorship clinic.
- Routine follow-up for HL survivors consists of history and directed physical examination with symptom-directed laboratory testing or imaging. Surveillance imaging and laboratory testing have not been shown to improve survival or to increase detection of relapsed disease.
- Monitoring for secondary malignancies and cardiovascular disease is a lifelong endeavor for HL survivors. Annual mammography is recommended starting 8 to 10 years after completion of treatment for women treated with chest or axillary radiation. Smoking cessation, cardiovascular risk assessment, and monitoring for hypothyroidism are recommended, particularly in patients receiving mediastinal or neck radiation. Referral to specialty survivorship clinics should be considered for HL survivors.

Bibliography

Introduction

Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-3277.

Hummel M, Anagnostopoulos I, Dallenbach F, Korbjuhn P, Dimmler C, Stein H. EBV infection patterns in Hodgkin's disease and normal lymphoid tissue: expression and cellular localization of EBV gene products. *Br J Haematol*. 1992;82(4):689-694.

Loddenkemper C, Anagnostopoulos I, Hummel M, et al. Differential Emu enhancer activity and expression of BOB.1/OBF.1, Oct2, PU.1, and immunoglobulin in reactive B-cell populations, B-cell non-Hodgkin lymphomas, and Hodgkin lymphomas. *J Pathol*. 2004;202(1):60-69.

Marafioti T, Hummel M, Foss HD, et al. Hodgkin and Reed-Sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. *Blood*. 2000;95(4):1443-1450.

Pilichowska M, Pittaluga S, Ferry JA, et al. Clinicopathologic consensus study of gray zone lymphoma with features intermediate between DLBCL and classical HL. *Blood Adv*. 2017;1(26):2600-2609.

Roemer MGM, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. *J Clin Oncol*. 2016;34(23):2690-2697.

Siegel R, Miller K, Fuchs H, et al. Cancer Statistics 2021. *CA Can J Clin*. 2021;71(1):7-33.

Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: increasing evidence of the importance of the microenvironment. *J Clin Oncol*. 2011;29(14):1812-1826.

Swerdlow SH, Campo E, Harris N. World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissues. IARC Press; 2008.

Clinical presentation, staging, and workup

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

Evens AM, Antillón M, Aschebrook-Kilfoy B, Chiu BC. Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis. *Ann Oncol*. 2012;23(8):2128-2137.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol*. 1989;7(11):1630-1636.

Mauch PM, Kalish LA, Kadin M, Coleman CN, Osteen R, Hellman S. Patterns of presentation of Hodgkin disease. Implications for etiology and pathogenesis. *Cancer*. 1993;71(6):2062-2071.

Purz S, Mauz-Körholz C, Körholz D, et al. [^{18}F]Fluorodeoxyglucose positron emission tomography for detection of bone marrow involvement in children and adolescents with Hodgkin's lymphoma. *J Clin Oncol*. 2011;29(26):3523-3528.

Frontline therapy for early-stage HL

André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin

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lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35(16):1786-1794.

Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet*. 2015;385(9976):1418-1427.

Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol*. 2004;22(14):2835-2841.

Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):640-652.

Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol*. 2003;21(19):3601-3608.

Fermé C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*. 2007;357(19):1916-1927.

Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. *J Clin Oncol*. 2019;37(31):2835-2845.

Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study Italian-Danish Study. *J Clin Oncol*. 2007;25(24):3746-3752.

Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2012;366(5):399-408.

Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372(17):1598-1607.

Raemaekers JMM, André MPE, Federico M, et al. Omitting radiotherapy in early positron emission tomography—negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2014;32(12):1188-1194.

Straus D, Jung S, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. *Blood*. 2018;132(10):1013-1021.

Frontline therapy for advanced-stage HL

Avigdor A, Bulvik S, Levi I, et al. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin's lymphoma. *Ann Oncol*. 2010;21(1):126-132.

Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2017;390(10114):2790-2802.

Borchmann P, Haverkamp H, Diehl V, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. *J Clin Oncol*. 2011;29(32):4234-4242.

Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378(4):331-344.

Eichenauer DA, Plütschow A, Kreissl S, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. *Lancet Oncol*. 2017;18(12):1680-1687.

Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol*. 2009;27(27):4548-4554.

Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379(9828):1791-1799.

Gallamini A, Tarella C, Viviani S, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. *J Clin Oncol*. 2018;36(5):454-462.

Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. *N Engl J Med*. 1998;339(21):1506-1514.

Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374(25):2419-2429.

Mounier N, Brice P, Bologna S, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. *Ann Oncol*. 2014;25(8):1622-1628.

Press OW, Li H, Schöder H, et al. US intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol*. 2016;34(17):2020-2027.

Skoetz N, Trelle S, Rancea M, et al. Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: a systematic review and network meta-analysis. *Lancet Oncol*. 2013;14(10):943-952.

Stephens DM, Li H, Schoder H, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. *Blood*. 2019;134(15):1238-1246.

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HL in older patients

Böll B, Goergen H, Behringer K, et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. *Blood*. 2016;127(18):2189-2192.

Cheson B, Bartlett N, LaPlant B, et al. Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma (ACCRU): a multicentre, single-arm, phase 2 trial. *Lancet Haematol*. 2020;7(11):e808-e815.

Engert A, Ballova V, Haverkamp H, et al. Hodgkin's lymphoma in elderly patients: a comprehensive retrospective analysis from the German Hodgkin's Study Group. *J Clin Oncol*. 2005;23(22):5052-5060.

Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. *J Clin Oncol*. 2018;36(30):3015-3022.

Friedberg JW, Forero-Torres A, Bordoni RE, et al. Frontline Brentuximab vedotin in combination with dacarbazine or Bendamustine in patients aged ≥60 years with HL. *Blood*. 2017; 130(26):2829-2837.

Zallio F, Tamiazzo S, Monagheddu C, et al. Reduced intensity VEPEMB regimen compared with standard ABVD in elderly Hodgkin lymphoma patients: results from a randomized trial on behalf of the Fondazione Italiana Linfomi (FIL). *Br J Haematol*. 2016;172(6):879-888.

Pediatric HL

Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol*. 2014;32(32):3651-3658.

Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992–2004). *Cancer*. 2008;112(2):416-432.

Metzger ML, Weinstein HJ, Hudson MM, et al. Association between radiotherapy versus no radiotherapy based on early response to VAMP chemotherapy and survival among children with favorable-risk Hodgkin lymphoma. *JAMA*. 2012;307(24):2609-2616.

Percy CL, Smith MA, Linet M, Ries LAG, Friedman DL. Lymphomas and reticuloendothelial neoplasms. In: Ries LAG, Smith MA, Gurney JG, et al, eds. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. National Cancer Institute; 1999:35-50.

Therapy for relapsed or refractory HL

Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. *J Clin Oncol*. 2018;36(14):1428-1439.

Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*. 2017;35(19):2125-2132.

Diefenbach CS, Hong F, Ambinder RF, et al. Ipilimumab, nivolumab, and brentuximab vedotin combination therapies in patients with relapsed or refractory Hodgkin lymphoma: phase 1 results of an open-label, multicentre, phase 1/2 trial. *Lancet Haematol*. 2020;7(9):e660-e670.

Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood*. 2017;130(2):221-228.

Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131(11):1183-1194.

Josting A, Kàtay I, Rueffer U, et al. Favorable outcome of patients with relapsed or refractory Hodgkin's disease treated with high-dose chemotherapy and stem cell rescue at the time of maximal response to conventional salvage therapy (Dexa-BEAM). *Ann Oncol*. 1998;9(3):289-295.

Kuruvilla J, Ramchandren R, Santoro A, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22(4):512-524.

Lavoie JC, Connors JM, Phillips GL, et al. High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: long-term outcome in the first 100 patients treated in Vancouver. *Blood*. 2005;106(4):1473-1478.

Merryman RW, Kim HT, Zinzani PL, et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. *Blood*. 2017;129(10):1380-1388.

Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;385(9980):1853-1862.

Moskowitz AJ, Schöder H, Yahalom J, et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosfamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. *Lancet Oncol*. 2015;16(3):284-292.

Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Blood*. 2010;116(23):4934-4937.

O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1–2 trial. *Lancet Oncol*. 2018;19(2):257-266.

Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica*. 2007;92(1):35-41.

Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med*. 2010;363(19):1812-1821.

Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell

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transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol*. 2016;17(9):1283-1294.

Follow-up of patients with HL

El-Galaly TC, Mylam KJ, Brown P, et al. PET/CT surveillance in patients with Hodgkin lymphoma in first remission is associated with low positive predictive value and high costs. *Haematologica*. 2012;97(6):931-936.

Goodman KA, Riedel E, Serrano V, Gulati S, Moskowitz CH, Yahalom J. Long-term effects of high dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(32):5240-5247.

Ng A, Constine LS, Advani R, et al. ACR appropriateness criteria: follow-up of Hodgkin's lymphoma. *Curr Probl Cancer*. 2010;34(3):211-227.

Sureda A, Arranz R, Iriondo A, et al. Autologous stem-cell transplantation for Hodgkin's disease: results and prognostic factors in 494 patients from the Grupo Español de Linfomas/Transplante Autólogo de Médula Ósea Spanish Cooperative Group. *J Clin Oncol*. 2001;19(5):1395-1404.

Nodular lymphocyte-predominant HL

Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol*. 2014;32(9):912-918.

Chen RC, Chin MS, Ng AK, et al. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. *J Clin Oncol*. 2010;28(1):136-141.

Eichenauer DA, Fuchs M, Pluetschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood*. 2011;118(16):4363-4365.

Nogová L, Reineke T, Brillant C, et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. *J Clin Oncol*. 2008;26(3):434-439.

Nogová L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). *Ann Oncol*. 2005;16(10):1683-1687.

Savage KJ, Skinnider BF, Al-Mansour M, Sehn LH, Gascoyne RD, Connors JM. Treating limited stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcomes. *Blood*. 2011;118(17):4585-4590.

Shankar A, Hall G, Gorde-Grosjean S, et al. Treatment outcome after low intensity chemotherapy (CVP) in children and adolescents with early-stage nodular lymphocyte predominant Hodgkin's lymphoma: an Anglo-French collaborative report. *Eur J Cancer*. 2011;48:1700-1706.

Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst*. 2007;99(3):206-214.

Wirth A, Yuen K, Barton M, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. *Cancer*. 2005;104(6):1221-1229.

Xing KH, Connors JM, Lai A, et al. Advanced-stage nodular lymphocyte predominant Hodgkin lymphoma compared with classical Hodgkin lymphoma: a matched pair outcome analysis. *Blood*. 2014;123(23):3567-3573.

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